

# Route of Administration

(Common Examples)

- Enteral
- Parenteral
- Inhalation
- Transdermal
- Ocular

# Mammalian System (Common Examples)

- GI Tract
- Brain
- Respiratory
- Skin
- Eye

# Absorption Barrier (Primary Barrier)

- Lumenal Tissue-Membrane
- Blood Brain Barrier Tissue-Membrane
- Nasal/Lung Tissue-Membrane
- Epidermal/Dermal Tissue-Membrane

Select Assay/Parameters Based on Route/Mammal/Barrier & Generate In vitro Bioavailability Data For Test Samples From Primary Library

# In vitro Bioavailability Assay/Data

Cell Culture/Tissue/Membrane Systems/SAR/QSAR

- Permeability
- (Transport Mechanism)\*

Physiological Fluid/Solvent/Buffer Systems/SAR/QSAR

- Solubility
- (Dissolution Rate)\*
- \*optional

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In vitro Bioavailability Data Provide In vitro Bioavailability Data to PK Tool/Select PK Model For Route/Mammal/Sampling Site PK Tool Input/Output System Simulation Engine Simulation Model Generate Absorption Profile for Each Test Sample at Validation/ Selected Sampling Site Optimization In vivo Absorption Profile Rate Extent Concentration Catalogue/Rank Test Samples & Generate Secondary Library Absorption Compound Library

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FIG. 4

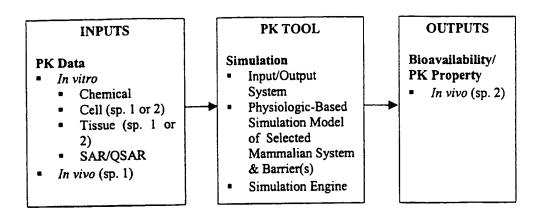


FIG. 5

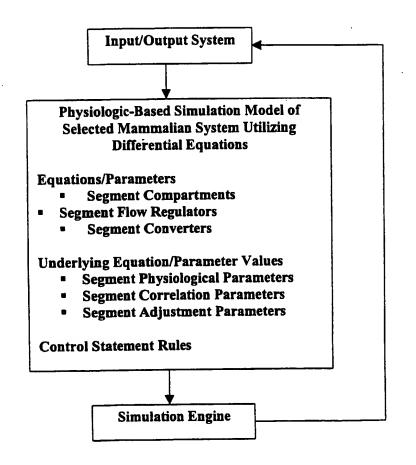


FIG. 6

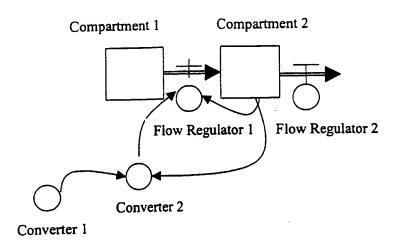


FIG. 7

Symbol	Name	Time-Dependent Function
	Compartment	Equation or value for amount of substance stored.
<b>→</b>	Flow Regulator	Rate equation for amount of substance transferred.
$\bigcirc$	Converter	Equation or pre-defined value for (i) input into flow regulator; (ii) input into another converter; and/or (iii) storing value.
$\sim$	Input Link	Directs input values.

FIG. 8

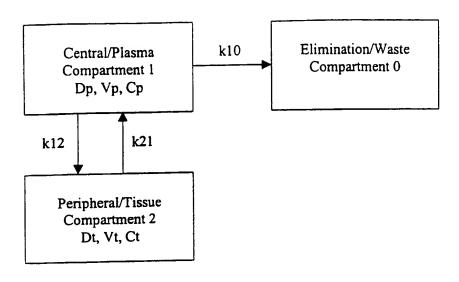


FIG. 9

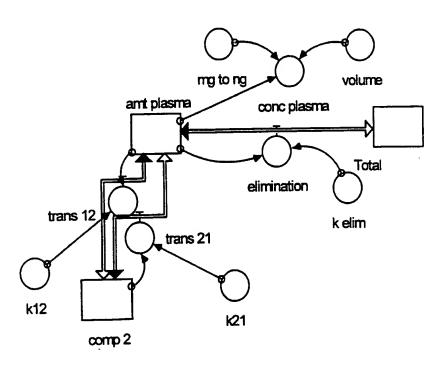


FIG. 10

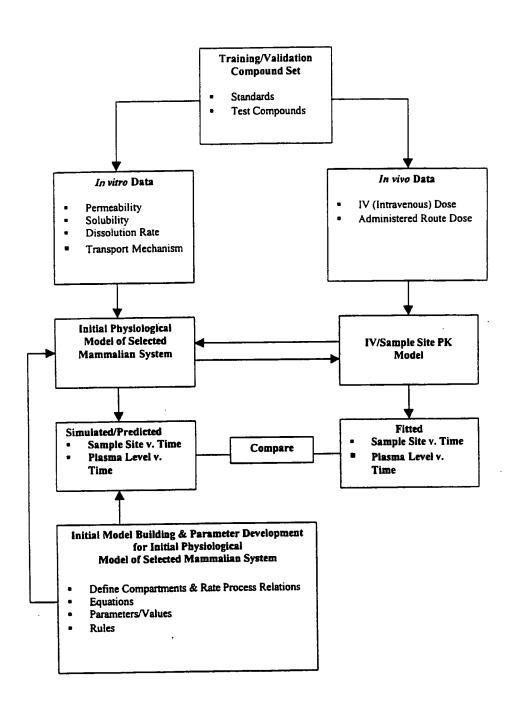
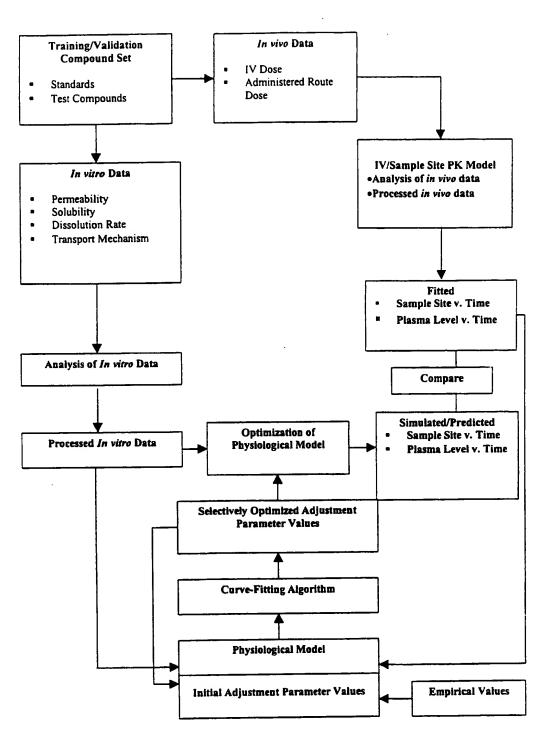
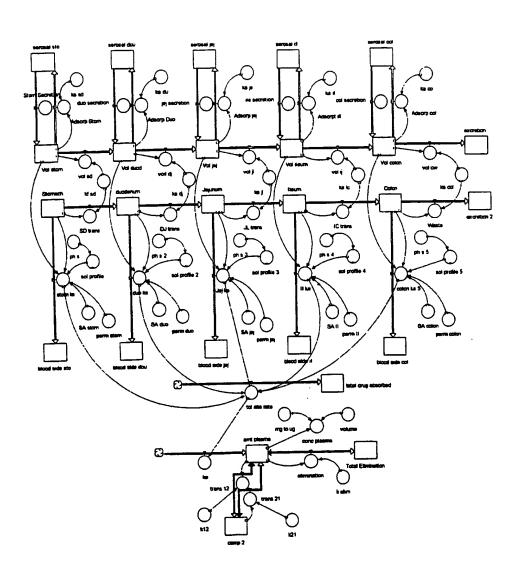


FIG. 11





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#### FIG. 13

## Mass-Volume GI Tract Model

# **GI Segment Compartments**

- Fluid Volume
- Fluid Absorption
- Insoluble Mass
- Soluble Mass Absorption

# GI Segment Flow Regulators

- Fluid Volume Absorption Rate
- Fluid Volume Secretion Rate
- Fluid Volume GI Transit Rate
- Insoluble Mass GI Transit Rate
- Soluble Mass Absorption Rate

# GI Segment Converters

- Rate Constant
- pΗ
- Solubility
- Surface Area
- Permeability

### FIG. 14

# Mass-Volume GI Tract Model

- GI Segment Compartments & Flow Regulators
  - Fluid Volume
    - Fluid Volume Absorption Rate
    - Fluid Volume Secretion Rate
    - Fluid Volume GI Transit Rate

  - Fluid Volume Absorption Fluid Volume Absorption Rate
    - Fluid Volume Secretion Rate
  - Insoluble Mass
    - Insoluble Mass GI Transit Rate
    - Soluble Mass Absorption Rate
  - Soluble Mass Absorption
    - Soluble Mass Absorption Rate

### FIG. 15

# Mass-Volume GI Tract Model

- GI Segment Flow Regulators & Converters
  - Fluid Volume Absorption Rate
    - Fluid Volume Absorption Rate Constant
  - Fluid Volume Secretion Rate
    - Fluid Volume Secretion Rate Constant
  - Fluid Volume GI Transit Rate
    - Fluid Volume GI Transit Rate Constant
  - Insoluble Mass GI Transit Rate
    - Insoluble Mass GI Transit Rate Constant
  - Soluble Mass Absorption Rate
    - Fluid Volume
    - Insoluble Mass
    - Mass Solubility Profile
      - pH
    - Permeability
    - Surface Area

**FIG. 16** 

### Mass-Volume GI Tract Model

- GI Segment Converters
  - Rate Constant
  - pH
  - Solubility
  - Surface Area
  - Permeability

FIG. 17

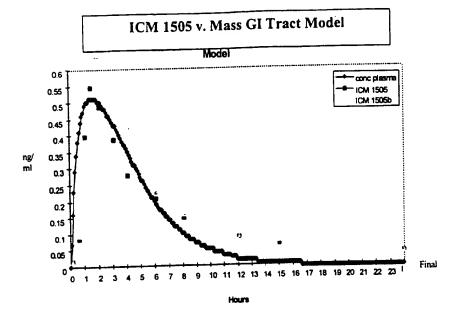
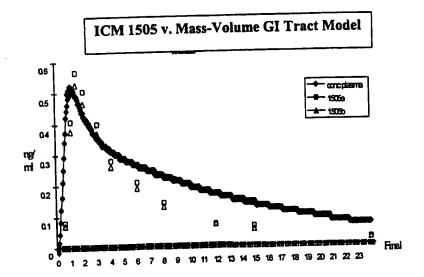
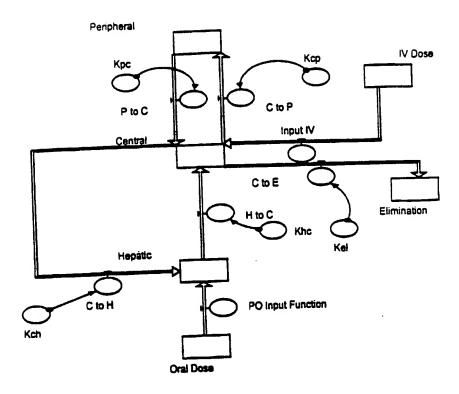


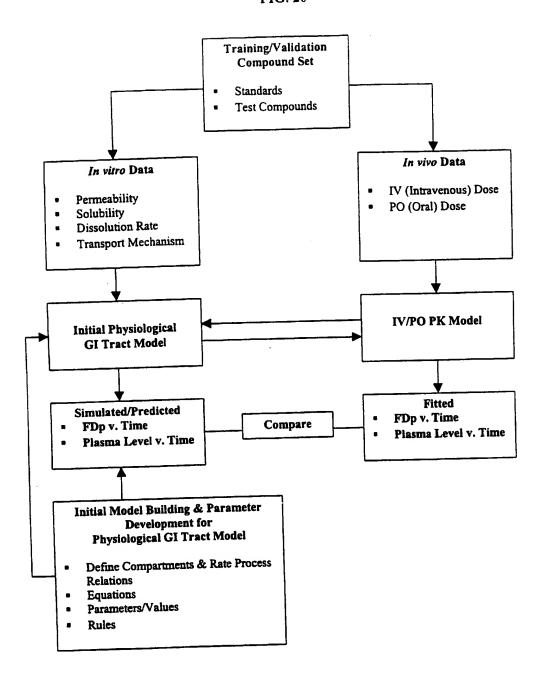
FIG. 18



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# Gastrointestinal Transit

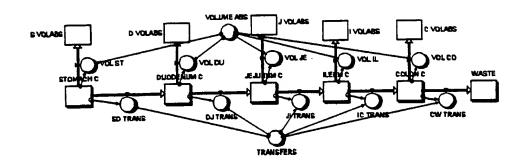
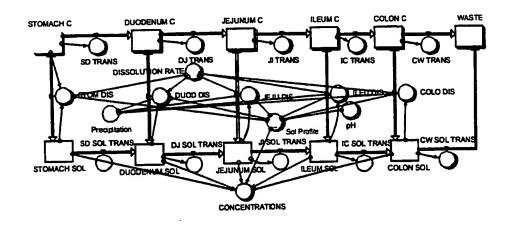


FIG. 22

pH Dependent Solubility and Dissolution



### FIG. 23

## Absorption

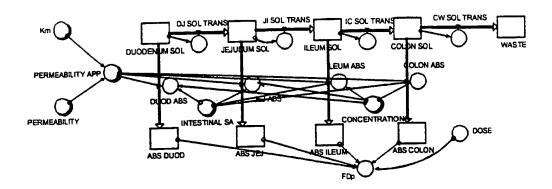
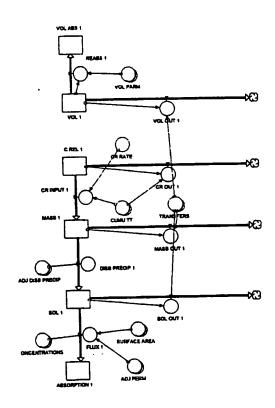
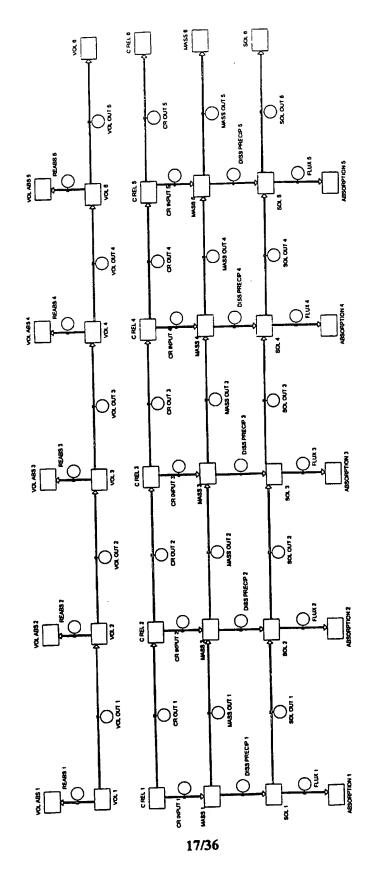


FIG. 24
GI Tract –Intestinal Model

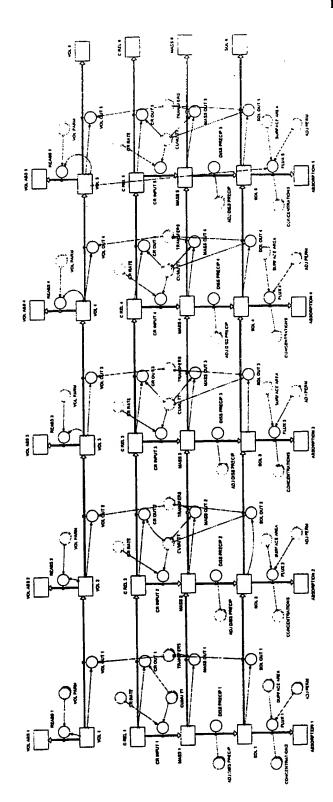


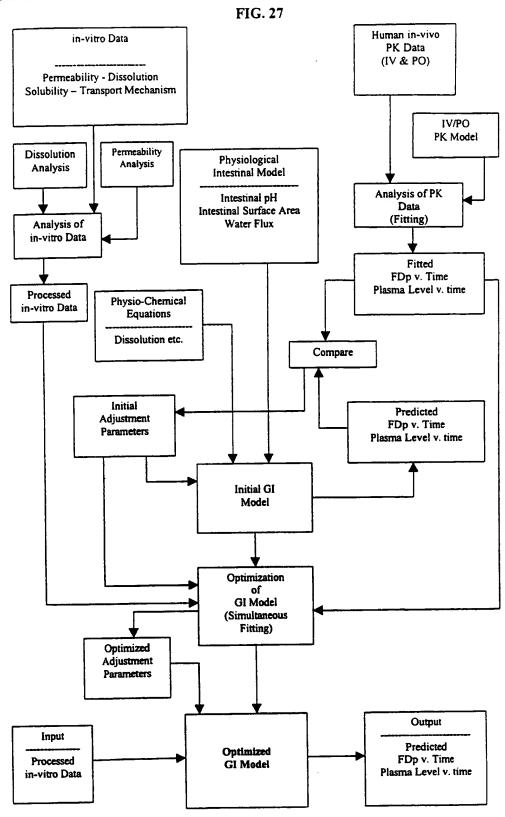
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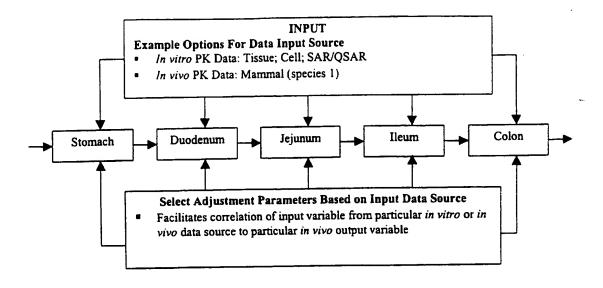
GI Tract-Intestinal Model (without converters, ghosts or connectors)

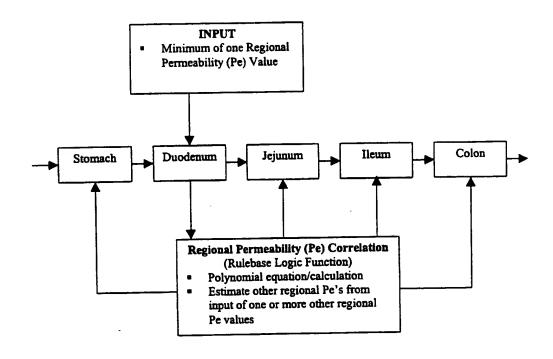


GI Tract-Intestinal Model











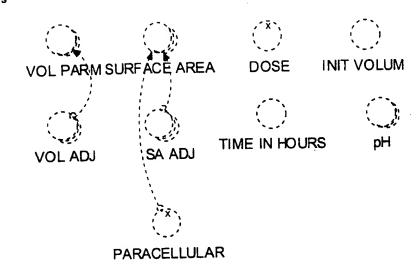


FIG. 31

### **Transit Time**

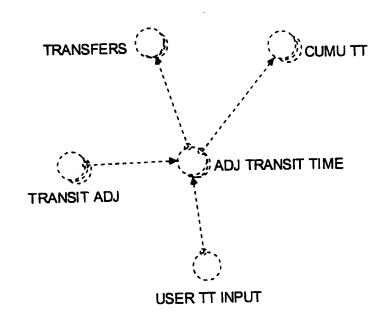


FIG. 32

# Permeability Calculation

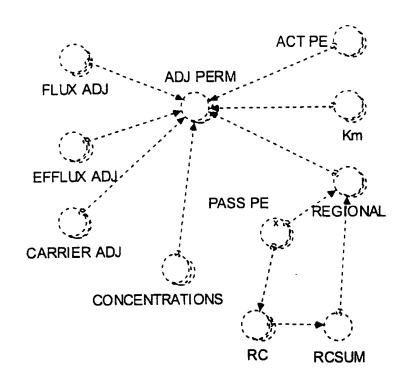
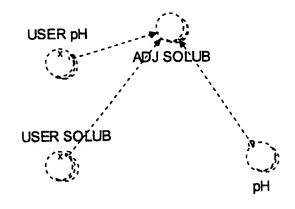


FIG. 33

## **Solubility Calculation**





## **Control Release Calculation**

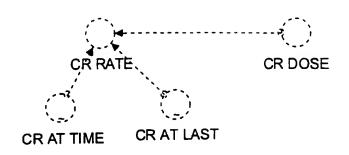


FIG. 35

### Concentration Calculation

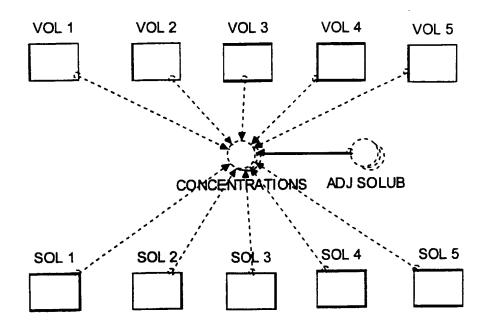


FIG. 36

### **Dissolution Calculation**

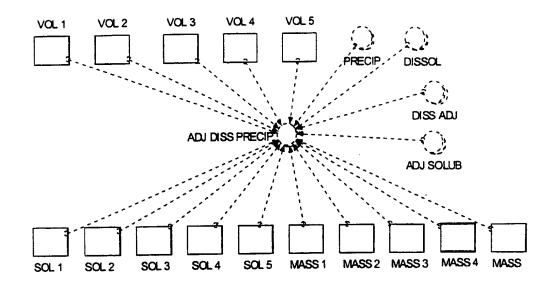


FIG. 37

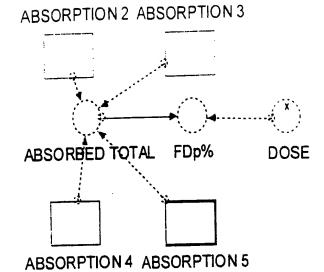
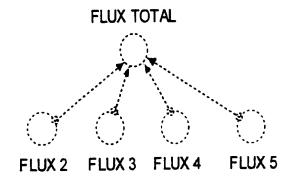


FIG. 38





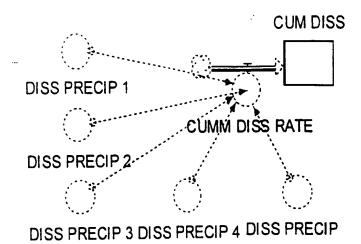
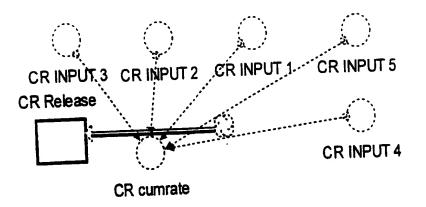


FIG. 40



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FIG. 41

### Physiological GI Tract Model

#### **Database**

- GI Segment Compartments
  - Fluid Absorption
  - Fluid Volume
  - Insoluble Mass
  - Soluble Mass
  - Soluble Mass Absorption
  - Dosage Form Mass

### GI Segment Flow Regulators

- Fluid Absorption Rate
- Fluid Volume Transit Rate
- Insoluble Mass Transit Rate
- Insoluble Mass Dissolution Rate
- Soluble Mass Transit Rate
- Soluble Mass Absorption Rate
- Dosage Form Disintegration/Release Rate

### GI Segment Converters

- Fluid Volume Absorption Rate Constant
- GI Transit Rate Constant
- Adjusted Dissolution Rate Constant
- Dissolved Drug Concentration
- Adjusted Surface Area
- Adjusted Permeability

### Rulebase

- GI Transit
- Dissolution
- Absorption
- Permeability Calculations
- Concentration Calculations
- Computational Error Corrections

#### FIG. 42

### Physiological GI Tract Model

- GI Segment Compartments & Flow Regulators
  - Fluid Absorption
    - Fluid Absorption Rate
  - Fluid Volume
    - Fluid Volume Absorption Rate
    - Fluid Volume Transit Rate
  - Insoluble Mass
    - Insoluble Mass Transit Rate
    - Insoluble Mass Dissolution Rate
  - Soluble Mass
    - Insoluble Mass Dissolution Rate
    - Soluble Mass Transit Rate
    - Soluble Mass Absorption Rate
  - Soluble Mass Absorption
    - Soluble Mass Absorption Rate

#### FIG. 43

### Physiological GI Tract Model

- GI Segments Flow Regulators & Converters
  - Fluid Absorption Rate
    - Fluid Volume
    - Fluid Volume Absorption Rate Constant
  - Fluid Volume Transit Rate
    - Fluid Volume
    - Fluid Volume Transit Rate Constant
  - Insoluble Mass Transit Rate
    - Insoluble Mass
    - Insoluble Mass Transit Rate Constant
  - Insoluble Mass Dissolution Rate
    - Insoluble Mass
    - Dissolution Rate Constant
  - Soluble Mass Transit Rate
    - Soluble Mass
    - Soluble Mass Transit Rate Constant
  - Soluble Mass Absorption Rate (Flux)
    - Surface Area
    - Dissolved Mass Concentration
    - Permeability

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### FIG. 44

# Physiological GI Tract Model

#### Converters

- Permeability
  - Passive Absorption Adjustment Parameter
    - Efflux/Secretion Adjustment Parameter
    - Active Absorption Adjustment Parameter
    - Active or Carrier Mediated Absorptive Permeability
    - Kn
    - Passive Permeability/Regional Correlation
      - Passive Permeability
      - Logic Function For Regional Correlation
        - Passive Permeability
        - Logic Function For Regional Correlation
    - Dissolved Mass Concentrations
- Dissolved Mass Concentration
  - Fluid Volume
  - Solubility
    - pH
    - Solubility
- Dissolution Rate Constant
  - Fluid Volume
  - Precipitation Rate Constant
  - Dissolution Rate Adjustment Parameter
  - Solubility
  - Insoluble Mass
  - Soluble Mass
- Surface Area
  - Surface Area Adjustment Parameter
  - Transport Mechanism
- Transit Rate
  - Transit Time Adjustment Parameter
  - User Adjusted Transit Time
- Fluid Volume Absorption Rate Constant
  - Fluid Volume Adjustment Parameter

FIG. 45

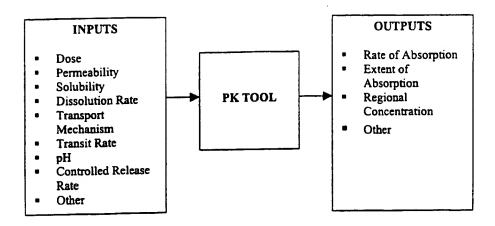
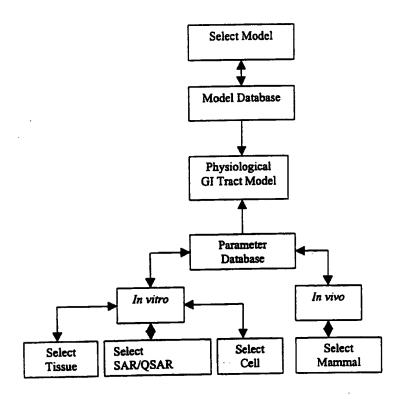
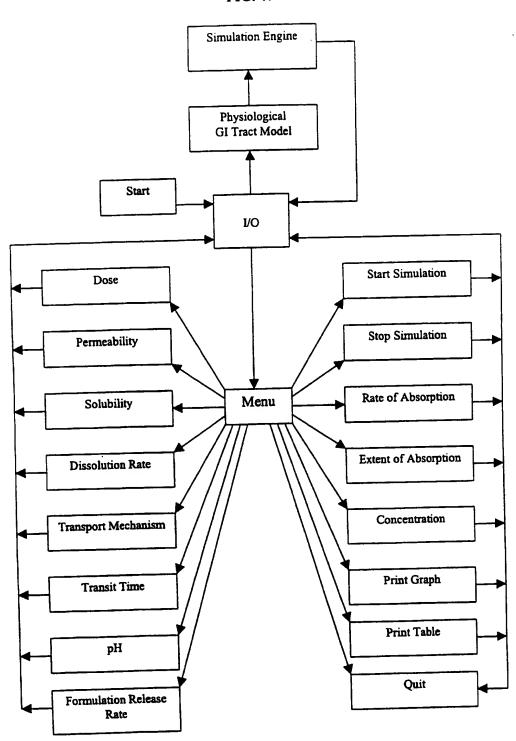


FIG. 46



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FIG. 47



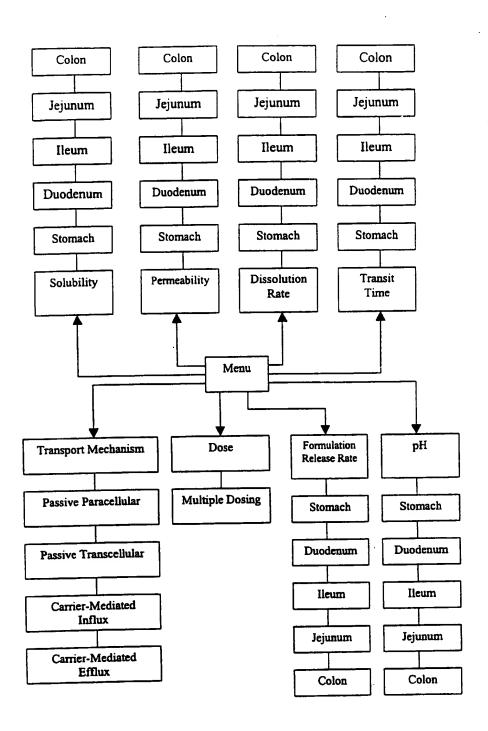


FIG. 49 Correlation of FDp Extent - GI Model and Pharmacokinetic data

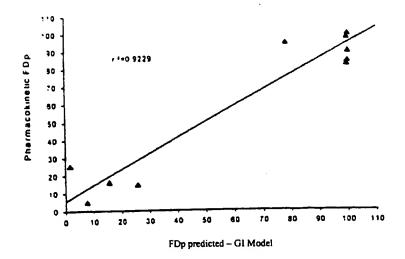


FIG. 50

Correlation of FDp rate of absorption - GI Model and Pharmacokinetic Data

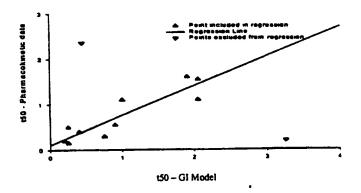


FIG. 51

PO Pharmacokinetic Data
Compound α I

Time (m)

Input From PK Fitting
Input From GI- Model
Oral Data

FIG. 52

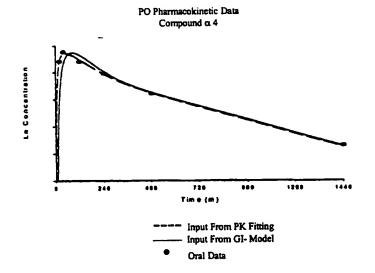
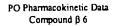
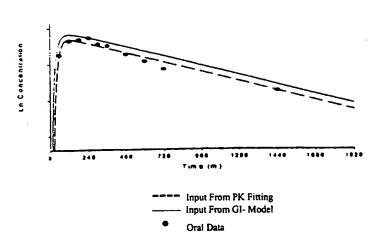


FIG. 53





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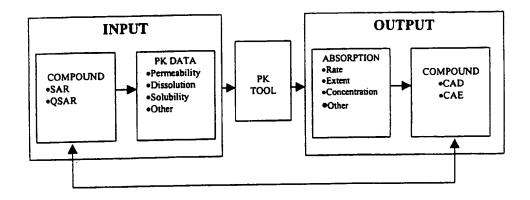


FIG. 55

